REMARKS

Telephonic Interview Request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Accordingly, Applicants herein submit an Applicant Initiated Interview Request Form. Applicants request the Examiner call Applicants' representative at (858) 720-7961 to set up a date and time to conduct the interview.

Telephonic Interview Summary

Applicants thank the Examiner for the very courteous and helpful telephonic interview with Applicants' representative Brenda J. Wallach, on July 17, 2007. Applicants have endeavored to amend the claims as discussed in that interview, as noted below, to place the claims in condition for allowance. If the Examiner has any additional questions or concerns, Applicants respectfully request that the Examiner call Applicants' representative, as requested above.

Status of the Claims

Claims 1 to 10 and 14 to 34 and 36 are pending. Claims 1-10, 14-30, and 32-33 have been amended. Claim 11-13 and 35 has been cancelled. Claims 37-39 have been added.

Accordingly, after entry of this amendment, claims 1 to 10, 14 to 34 and 36-39 will be pending and under consideration.

Claim Amendments

Claims 1-10, 14-30, and 32-33 have been amended to address the Examiner's objections and rejections, as set forth in the Office Action mailed April 19, 2007 and discussed in the interview of July 17, 2007. Claims 1-10, 14-30, and 32-33 have also been amended to correct grammatical and typographical errors.

The specification sets forth an extensive description of the invention as disclosed in the amended claims in this and previous responses. For example, support for amendments to the claims and for newly added claims 37-39 can be found at paragraphs 10, 11, 14, 17-22, 32, 36-39, 41-43, 46-48, 51-54 and 71 of this application's publication, specifically Publication No. US 2004/0203017 ("the '017 publication").

Accordingly, Applicants submit that no new matter has been introduced and the instant amendment can be properly entered.

Objections to the Specification

The office noted that "[t]he attempt to incorporate subject mater into this application by reference to a patent application is ineffective because incorporation by reference of essential material is only allowed when referring to published US applications or US patents." However, Applicants respectfully note they were not trying to incorporate the contents of paragraph 51 by reference.

In the Response of March 29, 2007, Applicants cited paragraph 51 of this application's publication (the '017 publication) for support of the claim amendments made in that Response. Applicants cited a paragraph of the published specification of the instant application instead of a page and line numbers of the specification as filed in an attempt to more clearly point out where support for the claim amendments could be found. Please note paragraph 51 of the '017 publication corresponds to page 14, line 27, to page 15 line 21 of this application.

Issues under 35 U.S.C. §112, first paragraph, written description

Claims 1 to 10 and 14 to 36, stand newly rejected under 35 U.S.C. §112, first paragraph, written description, for reasons set forth in detail on pages 3-5 of the OA. Applicants respectfully traverse the rejection of the claims.

The Office alleges that "[t]he specification as originally filed does not provide support for the invention as now claimed: 'and the at least first and second pseudotyped lentiviral vectors are designed to express no viral protein-encoding sequences and each express sequences comprising the polypeptide-encoding sequence of interest in either a sense or an antisense orientation' (claims 1, 21 and 22)". In addition, the Office alleges that the "instant claims now recite limitations which were not clearly disclosed in the specification as-filed..." (*see* pages 3 to 5 of the OA).

Applicants have removed the above language from claims 1, 21 and 22 and amended the claims as described below to address the Examiner's concerns and to overcome the written description rejection. In the telephonic interview of July 17, 2007, the Examiner requested that Applicants clearly point out where support for the amended claims can be found. This is provided

below.

Support for the phrase in claim 1 "wherein the polypeptide-encoding sequence of interest is a known or unidentified gene sequence"; the phrase in claim 21 "wherein the gene sequence of interest is known gene sequence"; and the phrase in claim 22 "wherein the gene sequence of interest is a known or unidentified gene sequence" is provided in the specification, for example, as indicated below. (Emphasis added.) Claims 1, 21, and 22 are the only independent claims. All other claims depend from claims 1 or 22.

The paragraph numbering is from the '017 publication, and the page and line number from the specification as filed are also included.

> **[0014]** "The present invention provides compositions and methods to increase the ability to identify one or more functions of products encoded by **unidentified gene sequences** or to further identify or confirm one or more functions of **known gene sequences**." (Emphasis added.) (page 4, lines 1-3 of the "Summary Section")
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> **[0017]** "Second, expression of the **unidentified or known gene sequence** is inhibited or terminated in a cell. Without limiting the scope of the invention, the inhibition may be by use of all or part of the gene sequence to recombine with the endogenous copy or copies of the sequence in said cell to terminate its expression." (Emphasis added.) (page 5, lines 19-22)
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> **[0037]** "The invention provides numerous advantages beyond the ability to identify one or more functions of **encoded gene products for which no activity is known**. These include the ability to provide additional information on the function of gene products for which **some activity information is already known**; the ability to provide information on the effect of over or under expressing one **functionless gene product** on the expression of another **functionless gene product**; and the ability to conduct the same analysis on different cell types which express different endogenous sequences." (Emphasis added.) (page 10, lines 8-14)
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> **[0038]** "The invention also provides a means for increasing the expression of **known gene products**. Once a gene sequence of interest has been found to increase expression of a desirable and known cellular gene product, the gene sequence of interest may be used at least to increase expression of the product for subsequent

isolation or purification." (Emphasis added.) (page 10, lines 15-18)

[0039] "It is a further advantage of the present invention that **there is no requirement for knowledge or speculation on the functionality of the gene of interest**. In embodiments of the invention where there is knowledge concerning the functionality of the gene of interest, the present invention advantageously provides means to identify one or more other functionalities that may have been previously unknown and/or to confirm one or more other functionalities that may have been previously known or suspected." (Emphasis added.) (page 10, lines 19-24)

[0042] "The present invention provides methods and compositions for the identification of one or more functionalities of the gene product of a given sequence. Preferably, the sequence is human, but one or more non-human sequences may also be used in combination with the present invention to identify their effect(s) on cellular factors in human cells. **Advantageously, there is no prerequisite for knowledge regarding the encoded functionality**. **If the functionality is known**, however, the present invention permits the confirmation of said functionality as well as the possible identification of previously unknown or unappreciated functionalities." (Emphasis added.) (page 11, line 18-25)

[0043] "In a preferred embodiment, the invention provides a vector for overexpressing a given **unidentified or known gene sequence** in a cell. Such expression is preferably under tight and/or inducible regulatory control. **An "unidentified" sequence is considered to not yet have confirmation of a cellular or biochemical functionality**." (Emphasis added.) (page 11, line 26-29)

[0052] "The given **unidentified or known gene sequence** to be over or under expressed **can be from any source and may even be partially identified**. Non-limiting examples of unidentified or partially identified sequences include those obtained from the isolation and characterization of EST (expressed sequence tag) sequences and any nucleic acid sequence considered to possibly encode a genes product whether RNA or proteinaceous in form. Such sequences include those identified by the assembly of EST sequences or otherwise determined to encode a gene product.

> These sequences include those that have undergone bioinformatics analysis and thus have homology to other known or uncharacterized sequences. By way of example, and without limiting the invention, a sequence encoding an open reading frame for which no function is assignable may be used in the present invention to identify one or more of its functions in a cell. Similarly, a sequence encoding an open reading frame with homology to a DNA binding protein (based on bioinformatics analysis for example) may be used in the present invention to confirm its putative functionality as a transcription factor." (Emphasis added.) (page 15, lines 23-31 and page 16, lines 1-5)

In addition, a long list of examples of the types of sequences that can be used in the present invention are provided below.

> **[0053]** "Non-limiting examples of known sequences may be from any source and include those for which one or more functionalities have been assigned. Such sequences include those in publicly available databases as well as any sequence for which the encoded gene product has been characterized. Such sequences may nevertheless be used in the present invention to confirm known functionalities and/or identify additional functionalities. By way of example, and without limiting the invention, a sequence encoding a kinase identified solely as phosphorylating a cytoplasmic protein may be found to cause elevated expression of a nuclear transcription factor upon overexpression of the kinase. Without being bound by theory, the kinase may directly or directly result in the increased expression of a transcription factor via its kinase activity. One possibility would be where the kinase phosphorylates the transcription factor to inactivate it, thereby causing an increase in its expression via a feedback loop. Other effects on cellular factors as described herein may also occur via one or more feedback loops." (page 16, lines 6-18)

> **[0054]** "Additionally, artificial sequences, such as recombinant fusion or other chimeric constructs as well as mutated versions of the sequences discussed above, may also be used in the present invention to identify their function(s). This aspect of the invention may be of particular advantage in the confirmation of a particular artificial protein or mutagenized protein as capable of substituting for the function(s) of a wildtype protein. For example, and without limiting the invention, a synthetic mutant version of the p53 protein which is able to multimerize with itself but not with

> dominant negative mutant forms of p53 may be used in the present invention to confirm its ability to substitute for wildtype functional p53. With such confirmation, the synthetic mutant may be used in therapeutic contexts to treat cells containing the dominant negative p53 mutation." (page 16, lines 19-28)

Support for the phrase in claim 1 "wherein the first lentiviral vector is designed to express little or no vector borne sequence other than the at least a part of the polypeptide-encoding sequence of interest", in claim 21 "wherein the pseudotyped lentiviral vector is designed to express little or no vector borne sequence other than the at least a part of the gene sequence of interest"; and in claim 22 "wherein the first lentiviral vector is designed to express little or no vector borne sequence other than the at least a part of the gene sequence of interest" is provided in the specification, for example, as indicated below.

Furthermore, support for the phrase in claim 1 "wherein the second lentiviral vector is designed to express little or no vector borne sequence other than the inhibitory or termination sequence"; and the phrase in claim 22 "wherein the second lentiviral vector is designed to express little or no vector borne sequence other than the inhibitory or termination sequence," is also provided in the specification, for example, as indicated below.

In addition, the following paragraphs not only provide support for the above phrases but also clearly explain the logic as to why the invention is designed to express little or no vector borne sequence *other* than the sequence of interest.

> **[0010]** "Another approach has been to make use of cell cultures to overexpress a gene sequence of interest.... Overexpression methods are, however, limited by the vector system used to deliver and express the gene. As an initial matter, known vector systems limit the number of cells that are transfected with the gene. For example, plasmid vectors have low transfection efficiencies and thus require the use of a selectable marker to isolate transfected cells. **But the expression of a marker gene from the plasmid vector tends to skew the phenotype detected because the gene of interest is not the only gene being overexpressed in the cell. Stated differently, expression of the gene of interest is not the only initial** perturbation **occurring in the cell. As such, the determination of gene function may be significantly mistaken due to skewing by expression of the marker gene**." (Emphasis added.) (page 3, lines 15-28)

[0011] "Higher transfection efficiencies are available from other viral vectors, such as **adenovirus based vectors**, but these vectors often fail to provide stable expression of the gene of interest. More importantly, such vectors **often have large numbers of their own genes to express** or suffer the risk of contamination due to co-infection by helper virus. **The expression of vector** and/or helper **virus genes** again **perturbs the intracellular environment and skews the detected phenotype and thus affects the determination of gene function**." (Emphasis added.) (page 3, line 29-31 (page 4, line 1-3)

[0014] "The present invention provides compositions and methods to increase the ability to identify one or more functions of products encoded by unidentified gene sequences or to further identify or confirm one or more functions of known gene sequences. Therefore, and in one aspect, the invention provides **a lentiviral vector capable of high transduction in primary cells, preferably without altering the overall gene expression profile of the cell, except for the expression of a specific payload encoding, or targeted to, one or more gene sequences under investigation**. Gene expression profile refers to the levels of expression, at the RNA and/or protein levels, of coding sequences in a cell." (Emphasis added.) (page 4, line 18-25)

[0022] "Preferably, the above over and underexpression of a gene sequence of interest is conducted by use of **a viral vector capable of high efficiency transduction without significant expression of endogenous** vector **gene sequences or helper virus contamination**." (Emphasis added.) (page 6, line 26-28)

[0043] "In a preferred embodiment, the invention provides a vector for overexpressing a given unidentified or known gene sequence in a cell. Such expression is preferably under tight and/or inducible regulatory control. An "unidentified" sequence is considered to not yet have been confirmed as having one or more cellular or biochemical functionalities. **Preferably, the overexpression occurs without simultaneous expression of other vector borne sequences, such as, but not limited to, selectable markers. Thus the intracellular environment is affected only by the overexpression of the sequence of interest** and the effects of said overexpression of the sequence of interest and the effects of said overexpression more accurately reflect one

> or more functionalities of said sequence." (Emphasis added.) (page 11, lines 26-29 and page 12, lines 1-6)
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> **[0051]** "Stable integration may be enhanced by stimulating the cells being transduced with an appropriate ligand followed by culturing the cells under standard conditions (see co-pending U.S. application Ser. No. 09/653,088 filed Aug. 31, 2000 and titled METHODS FOR STABLE TRANSDUCTION OF CELLS WITH VIRAL VECTORS, and allowed in June 2003) which is hereby incorporated in its entirety as if fully set forth. **Such vectors are also preferably designed to express little or no vector borne sequences other than the gene of interest**, whether in sense or antisense orientation." (Emphasis added.) (page 14, line 31 and page 15, lines 1-7)

Support for the phrase in claim 1 "a second pseudotyped lentiviral vector comprising an inhibitory or termination sequence, wherein the inhibitory or termination sequence can inhibit, terminate, or underexpress the endogenously expressed polypeptide-encoding sequence of interest"; and in claim 22 the phrase "a second pseudotyped lentiviral vector, comprising an inhibitory or termination sequence, wherein the inhibitory or termination sequence can inhibit, terminate, or underexpress the gene sequence of interest" is provided in the specification, for example, as indicated below:

> **[0017]** "Second, **expression of the unidentified or known gene sequence is inhibited or terminated in a cell**. Without limiting the scope of the invention, the **inhibition** may be by use of all or part of the gene sequence to recombine with the endogenous copy or copies of the sequence in said cell to terminate its expression." (Emphasis added.) (page 5, line 19-22)
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> **[0018]** "The vector is introduced into a cell for expression of the antisense sequence, which then binds to and results in the **inhibition of expression** of the complementary endogenous cellular sequence." (Emphasis added.) (page 5, line 30 and page 6, lines 1-2)
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> **[0019]** "Alternatively, polynucleotides corresponding or complementary to all or part of a gene sequence of interest may be used in the design or testing or use of polynucleotides for **post-transcriptional gene silencing** (PTGS)." (Emphasis added.) (page 6, lines 3-5)

[0020] "Therefore, the invention also provides for methods of **inhibition or termination of expression of a gene sequence** by the use of short (si) RNAs or ribozymes targeted against said sequences." (Emphasis added.) (page 6, lines 15-17)

[0021] "After expression of the antisense, ribozyme, or siRNA sequence(s) **to inhibit expression** of the complementary cellular sequence, changes in the expression, composition, or form of cellular factors as described above, in comparison to untreated normal cells, are detected and analyzed. This permits the identification of what cellular factors are affected by **decreasing or suppressing expression** of the endogenous cellular sequence corresponding to the gene of interest (complementary to the antisense sequence used)." (Emphasis added.) (page 6, lines 20-25)

[0022] "Preferably, the above over and **underexpression of a gene sequence of interest** is conducted by use of a viral vector capable of high efficiency transduction without significant expression of endogenous vector gene sequences or helper virus contamination." (Emphasis added.) (page 6, lines 26-28)

[0036] "The invention also provides methods for altering expression, composition, or form of one or more cellular factors in a cell by over expressing, **inhibiting** the expression of, or simultaneously **inhibiting** and overexpressing a gene sequence or sequences for which a function has been identified by the methods described above. Such methods may also be used to alter the phenotype of said cell." (Emphasis added.) (page 10, lines 3-7)

[0037] "The invention provides numerous advantages beyond the ability to identify one or more functions of encoded gene products for which no activity is known. These include the ability to provide additional information on the function of gene products for which some activity information is already known; the ability to provide information on the effect of over or **under expressing** one functionless gene product on the expression of another functionless gene product; and the ability to conduct the same analysis on different cell types which express different endogenous sequences." (Emphasis added.) (page 10, lines 8-14)

> **[0041]"FIG. 1** shows sample results when various sources of interest, "Seq" 1 to 4, are over or **under expressed**." (Emphasis added.) (page 11, lines 9-10)
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> **[0047]** "A variety of antisense sequences derived from various portions of the gene sequence to be **suppressed** may be used initially to determine which is most suitable for **decreasing the expression** of a cellular sequence." (Emphasis added.) (page 13, line 23-25)

Written description support for new claims 37-39.

Support for new claim 37 is provided in the specification, for example, as indicated below:

> **[0032]** "In another aspect of the invention, a high throughput, and optionally **computerized or robot implemented, system** for identifying gene function is provided." (Emphasis added.) (page 9, lines 6-7)
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> **[0071]** "An another aspect of the invention is the use of a high throughput system for the practice of the present invention. In one embodiment of this aspect, **the system maybe optionally computerized or robot implemented**, and may also include the use of the arrays described above." (Emphasis added.) (page 3, lines 3-6)

Support for new claim 38 is provided in the specification, for example, as indicated below:

> **[0019]** "Another form is via the use of small interfering RNAs (**siRNA**s) of less than about 30 nucleotides in double or single stranded form that induce PTGS in cells. A single stranded **siRNA** is believed to be part of an RNA-induced silencing complex (RISC) to guide the complex to a homologous MRNA target for cleavage and degradation. **siRNA**s induce a pathway of gene-specific degradation of target mRNA transcripts. **siRNA**s may be expressed in via the use of a dual expression cassette encoding complementary strands of RNA, or as a hairpin molecule." (Emphasis added.) (page 6, lines 8-14)
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> **[0020]** "Therefore, the invention also provides for methods of inhibition or termination of expression of a gene sequence by the use of short interfering **(si) RNAs** or ribozymes targeted against said sequences." (Emphasis added.) (page 6, lines 15-17)

> **[0021]** "After expression of the antisense, ribozyme, or **siRNA** sequence(s) to inhibit expression of the complementary cellular sequence, changes in the expression, composition, or form of cellular factors as described above, in comparison to untreated normal cells, are detected and analyzed." (Emphasis added.) (page 6, lines 20-23)

Support for new claim 39 is provided in the specification, for example, as indicated below:

> **[0018]**"Preferably, **the antisense sequence is ligated to co-localization sequences capable, upon expression with the antisense sequence, of co-localizing the antisense sequence with the complementary endogenous cellular, and 'sense', sequence**." (Emphasis added.) (page 5, lines 26-28)

> **[0048]** "While a variety of **co-localization sequences** may be used to co-localize the antisense molecule to the endogenous RNA, preferred sequences are the U1, U2, U3, U4, U5 or U6 snRNA, all of which may be operably linked to the above described antisense or ribozyme sequences. More preferably, the **co-localization sequence** used is a U1 snRNA/promoter cassette as described in Dietz (U.S. Pat. No. 5,814,500), which is hereby incorporated by reference in its entirety as if fully set forth." (Emphasis added.) (page 14, lines 1-6)

Issues under 35 U.S.C. §112, first paragraph, enablement

During the interview, the Examiner expressed a concern as to whether one skilled in the art at the time of the invention would have known how to make a lentiviral vector that is "designed to express little or no vector borne sequence" other than a sequence of interest, as in the claimed methods. Though working examples are not required for enablement, the Examiner was nonetheless concerned with the lack of examples in the specification that might provide guidance to one of skill in the art.

It was suggested by the Examiner that Applicants point to support within the specification where the making of such vectors is taught, and to submit a § 1.132 Declaration stating the one of skill in the art would have been able to practice the claimed invention at the time of the invention without undue experimentation. Such an expert declaration is provided herein, and Applicants have pointed to support within the specification showing that the making of such vectors with the

teaching of this disclosure could have been done by the skilled artisan without undue experimentation.

It should be noted that in one embodiment the novelty of the invention are the methods as claimed above, and that in this embodiment any pseudotyped lentiviral vector can be used to practice any of the claimed methods.

Applicants respectfully aver that one of skill in the art, together with the specification as filed, would have been able to practice the claimed invention without undue experimentation -in particular- to make and use vectors designed to express little or no vector borne sequence without undue experimentation. However, only to emphasize this point, and to illustrate the state of the art at the time of the invention, Applicants herein import text expressly incorporated by reference in the specification as filed.

Paragraph 20 of the specification as published (US 2004/0203017A1) refers to U.S. Patent No. 6,410,257 (hereinafter "the `257 patent"), and paragraph 85 expressly incorporates by reference all "references, including patents...."

Applicants will discuss below how the `257 patent teaches one of skill in the art how to make a vector that expresses little or no vector borne sequence other than the sequence of interest. It should be noted that the vector described in the `257 patent is only *an example* of *one* type of vector that can be used in the claimed methods.

The `257 patent discloses a vector that comprises at least one sequence to be expressed, wherein the sequence itself or the translation product of the sequence is useful in the treatment of a human disease. This sequence is the only sequence that is desired to be expressed in a cell, because it would *not* be desirable to express anything other than the sequence of interest if the vector is going to be put into a cell of a human for the treatment of HIV (*see* column 8, lines 8-10) or cancer (*see* column 22, lines 27-47). Column 7, line 63 to column 8, line 7, states that "a nonpathogenic, conditionally replicating vector...comprises at least one nucleic acid sequence...."

In addition, column 11, lines 19-24, of the the `257 patent discusses how a "conditionally replicating vector ... replicates only upon complementation with a wild-type strain of virus...." Furthermore, column 13, lines 3-36, describes how a conditionally replicating vector

> "lacks sequences encoding proteins that block superinfection with wild-type HIV (e.g., nef or env proteins) or comprises such

> sequence but they are either *not transcribed or not translated into functional protein*, such that their expression is deemed '*silent.*' Even more preferably, the vector *lacks the region or sequences coding the region of wild-type HIV from within the gag coding sequence to and including the nef gene*." (Emphasis added.)
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> It is further described how in "[e]xample 1 ... HIV, is cleaved using restriction enzymes to excise HIV encoding sequences from within the gag coding region to within the U3 region, following the nef gene.... The resultant vector produces a truncated gag transcript, and *does not produce wild-type Gag protein, or any other wild-type HIV proteins*. Moreover, it is not necessary that the vector express even the truncated gag protein inasmuch as the *gag translation initiation sequence can be mutated to prevent its translation*." (Emphasis added.)

Examples of retroviral vectors useful in the treatment of HIV are provided in Figures 1B-1E. In addition, Example 1 of the `257 patent, starting at column 29, line 55, to column 32, line 31, describes in detail the construction of a conditionally replicating vector.

The attached § 1.132 expert Declaration, signed by Dr. Laurent M. Humeau discusses how one skilled in the art, using the specification and teachings within, and the knowledge of one skilled in the art, would not have had to engage in undue experimentation to make the pseudotyped lentiviral vectors used in the method claims of the invention.

The following 29 paragraphs are taken directly from the § 1.132 expert Declaration of Dr. Laurent M. Humeau.

1. I, Laurent Michel Humeau, Ph.D., am an expert in the field of molecular biology and in particular in constructing and using lentiviral vectors for gene therapy, and was at the time of the invention. I am presently employed as Vice President of Research and Development at VIRxSYS Corporation, assignee of the above-referenced patent application. My resume is attached as documentation of my credentials (Exhibit A).

2. This Declaration is being filed in response to the Examiner's concerns regarding enablement that were brought up during an interview with Applicants' representative on July 17,

2007. During the interview, the Examiner expressed concern as to whether the skilled artisan at the time of the invention would know how to make a pseudotyped lentiviral vector that is "designed to express little or no vector borne sequence" other than a sequence of interest, as disclosed in the pending claims of the above-referenced application.

3. It was suggested by the Examiner that Applicants submit a § 1.132 Expert Declaration stating that with the teaching of this invention's disclosure one of skill in the art would have been able to practice the claimed invention at the time of the invention without undue experimentation.

4. It should be noted that the novelty of the invention is based, *inter alia*, on the novelty of the methods as claimed in the above-referenced application, and not on the novelty of the lentiviral vector used to practice the claimed method, and that *any* lentiviral vector, including any pseudotyped lentiviral vector, can be used to practice any of the claimed methods.

5. I declare that the skilled artisan, at the time of the invention, using the teachings of the specification and the knowledge known to the skilled artisan, would be able to make a pseudotyped lentiviral vector designed to express little or no vector borne sequence other than a sequence of interest using experiments that were routine experiments not empirical experimentation of trial and error. The routine nature of the experiments performed is described below.

6. To illustrate the state of the art at the time of the invention, Applicants herein import text expressly incorporated by reference in the specification.

7. Paragraph 20 of the specification as published (US 2004/0203017A1) refers to U.S. Patent No. 6,410,257 (hereinafter "the `257 patent"), and paragraph 85 expressly incorporates by reference all "references, including patents…."

8. The `257 patent teaches one of skill in the art how to make a vector that expresses little or no vector borne sequence other than the sequence of interest. It should be noted that the

vector described in the `257 patent is only *an example* of *one* type of vector that can be used in the claimed methods.

9. The `257 patent discloses a vector that comprises at least one sequence to be expressed, wherein the sequence itself or the translation product of the sequence is useful in the treatment of a human disease. This sequence is the only sequence that is desired to be expressed in a cell, because it would *not* be desirable to express anything other than the sequence of interest if the vector is going to be put into a cell of a human for the treatment of HIV (*see* column 8, lines 8-10) or cancer (*see* column 22, lines 27-47). Column 7, line 63 to column 8, line 7, states that "a nonpathogenic, conditionally replicating vector…comprises at least one nucleic acid sequence…."

10. In addition, column 11, lines 19-24, of the `257 patent discusses how a "conditionally replicating vector … replicates only upon complementation with a wild-type strain of virus…." Furthermore, column 13, lines 3-36, describes how a conditionally replicating lentiviral vector:

> "lacks sequences encoding proteins that block superinfection with wild-type HIV (e.g., nef or env proteins) or comprises such sequence but they are either *not transcribed or not translated into functional protein*, such that their expression is deemed '*silent*.' Even more preferably, the vector *lacks the region or sequences coding the region of wild-type HIV from within the gag coding sequence to and including the nef gene*." (Emphasis added.)

> It is further described how in "[e]xample 1 … HIV, is cleaved using restriction enzymes to excise HIV encoding sequences from within the gag coding region to within the U3 region, following the nef gene…. The resultant vector produces a truncated gag transcript, and *does not produce wild-type Gag protein, or any other wild-type HIV proteins*. Moreover, it is not necessary that the vector express even the truncated gag protein inasmuch as the *gag translation initiation sequence can be mutated to prevent its translation*." (Emphasis added.)

11. Examples of retroviral vectors useful in the treatment of HIV are provided in Figures 1B-1E of the `257 patent. In addition, Example 1, starting at column 29, line 55, to column 32, line 31, describes in detail the construction of a conditionally replicating lentiviral vector.

12. In addition to the teachings of the specification provided above, submitted herein are three articles (attached Exhibits B-D) that were published before the priority date of the current application, specifically January 25, 2001, showing that not only were many types of lentiviral vectors known at the time, but one skilled in the art knew how to design and manipulate such a vector.

13. **Kalpana, G.V., Retroviral Vectors for liver-directed gene therapy, Semin. Liver Dis. 19(1):27-37 (1999)** (hereinafter "Kalpana").

14. In Kalpana's review article, the principles underlying the design, construction, and use of retroviral vectors for gene therapy are discussed, with an emphasis on lentiviral vectors. The article describes how retroviruses are popular gene therapy vectors and how advances in the design of retroviral vectors have resulted in them being widely used in *ex vivo* gene therapy protocols (*see* Abstract). Page 27, second column, first full paragraph, describes how a thorough understanding of retroviral replication has helped in the design of efficient retroviral vectors.

15. The Kalpana article provides multiple examples of different types of lentiviral vectors and shows how it was common for one skilled in the art, at the time of the invention, to manipulate and generate various types of lentiviral vectors.

16. Page 28, second column, first paragraph, Kalpana describes how the most effective retroviral vectors are replication-defective viral vectors that are derived by manipulating the viral genome and by replacing most or all of the viral genes by therapeutic transgenes. Such manipulation is described in the second paragraph, specifically, "the therapeutic gene of interest is cloned into the transducing vector DNA that is 'crippled' or deleted of all the viral genes necessary for replication…."

17. On Page 31, first column, first full paragraph of Kalpana, self-inactivating retroviral (SIN) vectors are described. These vectors have been "handicapped", specifically, "a deletion introduced into the U3 region to remove enhancer and promoter elements at the 3' end of the transfer vector gets transmitted to the 5' region of the viral DNA in the recipient cell during reverse-transcription. When this viral DNA integrates, it lacks both 5' and 3' U3 regions, and thus is not able to initiate transcription from the viral LTRs."

18. Page 33, second column, first paragraph of Kalpana, describes how the best studied lentivirus is HIV-1, and how a crippled version of this virus has been developed into a lentiviral vector and has been used as a vehicle for *in vivo* gene delivery.

19. The generation of lentiviral vectors is discussed further on page 34, first column, second full paragraph of Kalpana. Lentiviral vectors are described in which the transgene of interest is inserted between the LTRs and the packaging signal. In addition, the vector is pseudotyped with VSV-G to obtain a broad host cell range.

20. On page 35, first column, first full paragraph of Kalpana, second- and third-generation lentiviral vectors are described wherein many of the accessory proteins are removed from the vectors. Furthermore, if is discussed how by introducing mutations or deletions into the vector, four of the accessory proteins that are not essential for vector-mediated transduction were eliminated. The replacement of a native promoter present in the U3 region of LTR with a constitutive promoter, such as CMV, is also described.

21. On page 35, under the section entitled "Perspectives" the Kalpana describes how retroviral vectors offer great potential for gene therapy and how out of several hundred clinical gene therapy trials currently ongoing, more than 45% are using retroviral vectors. Furthermore, it is stated how "the current improvements in lentiviral vectors eliminate the possibility of regenerating RCR and thus are excellent biosafety measures." In the last paragraph of page 35, the authors note how "[a]nother flexibility of retroviral vectors is that they can be pseudotyped with envelopes from other viruses, thus expanding the possibility of host range."

22. Thus, Kalpana explains how because of the thorough understanding of retroviral replication and the structure of viral RNA, skilled artisans were able to design, manipulate, and create lentiviral vectors that are safe enough for use in gene therapy trials.

23. **Naldini, L., In vivo gene delivery by lentiviral vectors, Thromb. Haemost., 82(2):552-554 (1999)** (hereinafter "Naldini").

24. Page 552, first column of Naldini, starting at the last paragraph, describes the design and construction of a hybrid lentiviral vector comprising a core derived from HIV-1, thus maintaining the ability of the lentiviruses to infect non-dividing cells, combined with the envelope of another virus.

25. On Page 552, second column, second full paragraph, Naldini discusses how they "embarked on the identification of the minimal genetic information required for transduction. All HIV-1 sequences found unnecessary were eliminated from the constructs used to generate the vectors." The last paragraph on page 552 describes how the authors were able to successfully eliminate the nonessential sequences from the constructs used to generate the vector.

26. Thus, Naldini supports that at the time of this invention it was routine for the skilled artisan to manipulate the sequences of HIV-1 in order to design a lentiviral vector.

27. **Wong-Staal, F., *et al.*, Development of HIV vectors for anti-HIV gene therapy, Proc. Natl. Acad. Sci. USA, 93(21):11395-11399 (1996).** (hereinafter "Wong-Staal")

28. On Page 11397, second paragraph of Wong-Staal, starting at the last paragraph, the authors describe the construction of HIV-1 and HIV-2 based lentiviral vectors. Among other things, it is discussed how various manipulations to the retroviral vectors are conducted: a 5' LTR is linked to a leader sequence; a marker gene is inserted; and in some vectors an element from Mason-Pfizer monkey virus was inserted in place of an RRE. These are all examples of how one skilled in the art was able to design, manipulate and construct lentiviral vectors.

29. In summary, the skilled artisan at the time of the invention, based on the teachings of the specification and the knowledge and methods known at the time of the invention, would have known how to routinely design and make a pseudotyped lentiviral vector that is "designed to express little or no vector borne sequence" other than a sequence of interest, as disclosed in the pending claims of the above-referenced application. Lastly, one skilled in the art would not have to engage in undue experimentation to make and use the claimed invention in its full scope – particularly with respect to making and using a lentiviral vector to practice this claimed invention.

In light of the arguments provided above and in the attached Declaration and Exhibits A-D, and the amendments to claims 1, 21, and 22, Applicants respectfully maintain that all of the Office's concerns have been addressed, and that the rejections under 35 U.S.C. §112, first paragraph, written description and enablement, can be properly withdrawn.

Issues under 35 U.S.C. §112, second paragraph

Claims 1 to 10 and 14 to 36, are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for reasons set forth in detail on page 5 of OA. Applicants respectfully traverse the rejection of the claims.

It was alleged that the phrase "the at least first and second pseudotyped lentiviral vectors are designed to express no viral protein-encoding sequences and each express sequences comprising the polypeptide-encoding sequence of interest in either a sense or an antisense orientation" is vague and indefinite.

Applicants believe that the amendments to independent claims 1, 21, and 22 presented above address the Office's concerns, and the rejection under 35 U.S.C. §112, second paragraph, can be properly withdrawn. All other rejected claims are dependent from either claim, 1, 21, or 22.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the objection to the specification, and rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs. The amendment places the case in condition for allowance, does not raise any issues of new matter, and the amended claims do not present new issues requiring further consideration or search. Applicants respectfully submit that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing Docket No. **397272000500**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephonic interview after the Examiner has reviewed the instant response and amendment.

Dated: October 19, 2007

Respectfully submitted,

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